Answer 1:

Bibliographic Information

Improved tumor targeting of anti-epidermal growth factor receptor Nanobodies through albumin binding: taking advantage of modular Nanobody technology. Tijink, Bernard M.; Laeremans, Toon; Budde, Marianne; Stigter-van Walsum, Marijke; Dreier, Torsten; de Haard, Hans J.; Leemans, C. Rene; van Dongen, Guus A. M. S. Departments of Otolaryngology/Head and Neck Surgery and Nuclear Medicine and PET Research, Amsterdam, VU University Medical Center, The Netherlands and Ablynx NV, Ghent, Belg. Molecular Cancer Therapeutics (2008), 7(8), 2288-2297. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. AN 2008:1017202 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The .apprx.15-kDa variable domains of camelid heavy-chain-only antibodies (called Nanobodies) can easily be formatted as multivalent or multispecific single-chain proteins. Because of fast excretion, however, they are less suitable for therapy of cancer. In this study, we aimed for improved tumor targeting of a bivalent anti-epidermal growth factor receptor (EGFR) Nanobody (αEGFR-αEGFR) by fusion to a Nanobody unit binding to albumin (αAlb). Biodistributions of αEGFR-αEGFR, αEGFR-αEGFR-αAlb (.apprx.50 kDa), αTNF-αTNF-αAlb (control, binding tumor necrosis factor-α), and the .apprx.150-kDa anti-EGFR antibody cetuximab were compared in A431 xenograft-bearing mice. The proteins were radiolabeled with 177Lu to facilitate quantification. Tumor uptake of 177Lu-αEGFR-αEGFR decreased from 5.0 ± 1.4 to 1.1 ± 0.1 %ID/g between 6 and 72 h after injection. Due to its rapid blood clearance, tumor-to-blood ratios >80 were obtained within 6 h after injection. Blood clearance became dramatically slower and tumor uptake became significantly higher by introduction of αAlb. Blood levels of αEGFR-αEGFR-αAlb were 21.2 ± 2.5, 11.9 ± 0.6, and 4.0 ± 1.4 and tumor levels were 19.4 ± 5.5, 35.2 ± 7.5, and 28.0 ± 6.8 %ID/g at 6, 24, and 72 h after injection, resp. Tumor uptake was at least as high as for cetuximab (15.5 ± 3.9, 27.1 ± 7.9, and 25.6 ± 6.1 %ID/g) and significantly higher than for αTNF-αTNF-αAlb. αEGFR-αEGFR-αAlb showed faster and deeper tumor penetration than cetuximab. These data show that simple fusion of αEGFR and αAlb building blocks results in a bifunctional Nanobody format, which seems more favorable for therapy as far as pharmacokinetics and tumor deposition are concerned. [Mol Cancer Ther 2008;7(8):2288-97].

Answer 2:

Bibliographic Information

Delayed type hypersensitivity-associated cytokines in islet xenotransplantation: limited efficacy of interleukin-2- and tumor necrosis factor-alpha-blockade in interferon-gamma receptor-deficient mice. Benda B; Lycke N; Holstad M; Korsgren O Department of Oncology, Radiology, and Clinical Immunology, Uppsala University, Sweden Xenotransplantation (2000), 7(3), 206-13. Journal code: 9438793. ISSN:0908-665X. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 11021666 AN 2000465742 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

To investigate the role of interferon (IFN)-gamma and tumor necrosis factor (TNF)-alpha and their potential to replace each other in the process of fetal porcine islet-like cell cluster (ICC) xenograft rejection, mice with a targeted disruption of the IFN-gamma receptor gene and wild-type controls were transplanted with fetal porcine ICCs under the kidney capsule and given post-transplant treatment with the TNF-alpha-inhibiting agent MDL 201,449A. Some of the MDL 201,449A-treated IFN-gamma receptor-deficient mice received additional treatment with cyclosporinee (CsA). Evaluation of the xenografts was performed 7 days after transplantation (all groups), and in IFN-gamma receptor-deficient mice treated with MDL 201 449 A, also 10 and 13 days after transplantation. On day 7 after transplantation, a few CD3+ cells were seen accumulated peripherally in the ICC xenograft. Moderate to abundant numbers of F4/80+ and Mac-1+ cells surrounded a few remaining ICCs present within the xenograft. Histochemical visualization of cyanide-resistant endogenous peroxidase activity for detection of eosinophils demonstrated only small numbers of eosinophils present within the xenograft by day 7 after transplantation. An increased amount of eosinophilic granulocytes was not found until

day 10 after transplantation, i.e. at a time when ICC xenograft rejection has already been completed. However, two out of six IFN-gamma receptor-deficient mice given post-transplant treatment with CsA and MDL 201,449A exhibited intact ICC xenografts with ICCs arranged in chords and duct-like structures on day 7 after transplantation. Taken together, findings in this study indicate that, in the pig-to-mouse model, IFN-gamma, TNF-alpha, and interleukin-2 seem to be of importance to fetal porcine ICC xenograft rejection. Nevertheless, in a majority of animals, other cytokines eventually substitute for the lack of IFN-gamma, TNF-alpha and interleukin-2.

Answer 3:

Bibliographic Information

Lack of antitumour activity of human recombinant tumour necrosis factor-alpha, alone or in combination with melphalan in a nude mouse human melanoma xenograft system. Furrer M; Altermatt H J; Ris H B; Althaus U; Ruegg C; Lienard D; Lejeune F J Department of Thoracic and Cardiovascular Surgery, University of Bern, Switzerland Melanoma research (1997), 7 Suppl 2 S43-9. Journal code: 9109623. ISSN:0960-8931. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 9578416 AN 1998237527 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The most promising developments in the field of isolated limb perfusion have centred around the use of the recombinant cytokine tumour necrosis factor-alpha (rTNF-alpha) in combination with melphalan. While the results of clinical trials are impressive, the exact antitumour mechanisms of rTNF-alpha and its role in combination with melphalan remain unclear. Our aim was to study the antitumour activity of human rTNF-alpha with or without the combination of melphalan in a nude mouse human melanoma xenograft system. In a first attempt to define the maximal tolerated single dose of rTNF-alpha in this setting, 15 animals were exposed to increasing doses of rTNF-alpha (60-2500 microg/kg intraperitoneally). All but one animal survived and tumour growth was not influenced by these single dose applications of rTNF-alpha even at the very high doses. Anti-tumour activity of repeated application of melphalan (three times 9 mg/kg in group 2 and three times 6 mg/kg in group 3), of rTNF-alpha alone (nine doses of 50 microg/kg in group 4), and of rTNF-alpha in combination with melphalan (nine doses of 50 microg/kg rTNF-alpha and three times 6 mg/kg melphalan in group 5) was further compared with non-treated animals (group 1). Tumour growth was significantly inhibited in all animals treated with melphalan (group 2, 3 and 5), but was not decreased in animals treated with rTNF-alpha alone (group 4). Mean final tumour volumes and mean tumour weight were not different in group 2 (789 +/- 836 mm3, 0.38 +/- 0.20 g), group 3 (1173 +/- 591 mm3, 0.55 +/- 0.29 g) and group 5 (230 +/- 632 mm3, 0.37 +/- 0.29 g), but significant lower than group 1 (3156 +/- 1512 mm3, 2.35 +/- 0.90 g) and group 4 (3228 +/- 1990 mm3, 2.00 +/- 1.16 g). There were no significant differences between high and low dose melphalan treatment and between melphalan treatment in combination with rTNF-alpha.

Histological examination did not show differences between treated and non-treated animals besides slightly inhibited mitotic activities of tumour cells in melphalan-treated animals. While tumour growth of human xenotransplanted melanoma in nude mice could be inhibited by melphalan, we failed to demonstrate any antitumour effect of rTNF-alpha. The combination of melphalan and rTNF-alpha did not enhance the antiproliferative effect of melphalan alone. Human xenotransplanted tumours on nude mice might not be the ideal experimental setting for studies of potential direct antineoplastic activity of rTNF-alpha, and these results support the concept that TNF-alpha exerts its antitumour activity indirectly, possibly by impairing the tumour vasculature and by activating the immune system.

Answer 4:

Bibliographic Information

Cryptosporidium parvum infection of human intestinal xenografts in SCID mice induces production of human tumor necrosis factor alpha and interleukin-8. Seydel K B; Zhang T; Champion G A; Fichtenbaum C; Swanson P E; Tzipori S; Griffiths J K; Stanley S L Jr Department of Molecular Microbiology, Washington University School of Medicine, St. Louis, Missouri 63110, USA Infection and immunity (1998), 66(5), 2379-82. Journal code: 0246127. ISSN:0019-9567. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in

English. PubMed ID 9573136 AN 1998234080 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The protozoan parasite Cryptosporidium parvum invades intestinal epithelial cells and can cause life-threatening diarrhea in immunocompromised individuals. Despite the clinical importance of this organism, much remains to be learned about the pathogenesis of C. parvum-induced diarrhea. To explore the role of the intestinal inflammatory response in C. parvum disease, using C. parvum oocysts we infected human intestinal xenografts in severe combined immunodeficient (SCID) mice. Seven days after infection, we found levels of human tumor necrosis factor alpha and interleukin-8 in C. parvum-infected human intestinal xenografts that were significantly higher than those seen in uninfected control xenografts. These results demonstrate that human intestinal cells produce proinflammatory cytokines in response to C. parvum infection and establish SCID-HU-INT mice as a model system to study the interactions of C. parvum with the human intestine.

Answer 5:

Bibliographic Information

Regression of human breast cancer xenografts in response to intralesional treatment with interferons alpha and gamma potentiated by tumor necrosis factor. Ozzello L; de Rosa C M; Cantell K; Kauppinen H L; Habif D V Sr Department of Pathology, Columbia University, College of Physicians and Surgeons, New York, NY 10032, USA Journal of interferon & cytokine research : the official journal of the International Society for Interferon and Cytokine Research (1995), 15(10), 839-48. Journal code: 9507088. ISSN:1079-9907. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 8564705 AN 1996122470 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The potentiating effects of human recombinant tumor necrosis factor-alpha (rTNF-alpha) on the antitumor actions of recombinant interferon-gamma (rIFN-gamma) and of natural interferons alpha and gamma combined (nIFN-alpha/nIFN-gamma) were studied on human breast cancer xenografts growing bilaterally in nude mice. The cytokines were injected singly or in combination in one of the two tumors of each mouse to study local effects while the opposite tumor was left undisturbed to evaluate systemic effects. The tumors received 20 intralesional injections (four cycles of 5 daily injections each). In injected tumors the best results were obtained with nIFN-alpha/nIFN-gamma supplemented with rTNF-alpha. The responses were dose dependent, resulting in complete regression of 9 of 9 tumors with rTNF-alpha used at the dose of 5 micrograms per injection, of 6 of 8 tumors at the dose of 2.5 micrograms, and of 4 of 8 tumors at the dose of 0.5 microgram. Mostly mild to moderate partial responses were seen in the other groups. The systemic effects on the contralateral tumors were significantly less than the local effects on the corresponding tumors. Histologically, responding tumors showed reactive fibrosis and inflammatory cell infiltration. No vascular alterations were seen, presumably because of the immunodeficiency of nude mice. It was concluded that the potentiation of the antitumor actions of IFNs by rTNF-alpha was effective at the local but not at the systemic level.

Answer 6:

Bibliographic Information

Treatment with tumor necrosis factor alpha and interferon alpha of a human kidney cancer xenograft in nude mice: evidence for an anticachectic effect of interferon alpha. Bassukas I D; Hofmockel G; Maurer-Schultze B Institute of Medical Radiation Research, University of Wurzburg, Germany Anticancer research (1994), 14(1A), 237-45. Journal code: 8102988. ISSN:0250-7005. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 8166454 AN 1994219821 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Unfortunately the efficacy of the treatment of the metastatic or recurrent renal cell carcinoma (RCC) has not improved during the last few years. Recently effort has been put into the experimental and clinical evaluation of so-called "biological response modifiers" (BRM; cytokines and related peptides) as treatment modalities for RCC. The present results are, however, still disappointing. Since BRM, if applied alone, are largely ineffective as antineoplastic agents, more experimental studies are now necessary to test the antineoplastic value of their combinations, which seem to be more promising. In the present study, the in vivo effect of tumor necrosis factor a (TNF a) and/or interferon a (IFN a) on the macroscopic tumor growth (external caliper measurements of tumor size) and on the cell proliferation (in vivo 3H-thymidine labelling index, LI, and mitotic index, MI) of a human RCC xenograft line in nude mice has been investigated. Neither of these substances alone nor their combination was effective in changing the time course of the tumor sizes and the growth patterns of the treated tumors in a statistically significant manner as compared to the untreated controls. Also the cell kinetic parameters were only marginally affected by these treatments, whereby TNF a alone proved to be more effective than IFN a alone. However, compared to the effect of TNF alpha alone, the combination with IFN alpha leads to some amelioration of the cell kinetic perturbations and also to an appreciable shift in the growth patterns of the tumors from distinct Gompertzian (under TNF alpha alone) to near exponential (under the combination treatment; $p < 0.05$). As a consequence, the tumors grow more slowly under the combined treatment during the observation time, and on the other hand, their growth does not decelerate as much as under TNF alpha alone.

Actually, if tumor growth continues in the same way, the extrapolation of the present data predicts smaller and greater tumors than the control tumors in the TNF alpha and in the combination treatment groups respectively. Notably, in the combination the effect of the IFN alpha seems to predominate. This is also seen in the effect of this combination on the cachexia of these tumor-bearing animals: either alone or in combination with TNF alpha, IFN alpha partially protects the animals from tumor-growth associated weight loss. Although the direct antineoplastic in vivo effect of the present cytokine combination against this human RCC xenograft line is rather limited, the potential antagonizing effect of IFN alpha on the development of cachexia should be further explored.

Answer 7:

Bibliographic Information

Treatment of a human renal cell carcinoma in nude mice with recombinant human tumor necrosis factor alpha and etoposide. Hofmockel G; Bassukas I D; Heimbach D; Wirth M; Maurer-Schultze B Department of Urology, University of Wurzburg, Germany The Journal of urology (1993), 150(6), 1974-9. Journal code: 0376374. ISSN:0022-5347. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 8230548 AN 1994047459 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The effect of treating a human renal cell adenocarcinoma xenografted into Balb/c-nu/nu (nude) mice with recombinant human tumor necrosis factor alpha (TNF alpha) and the cytostatic agent etoposide (ETP) as monotherapy or combination has been studied. Antitumor effects were evaluated by determining growth of the tumor implants by external caliper measurements and tumor cell proliferation by determining the labelling index (LI) after pulse labelling with 3H-thymidine. The toxicity of the treatment with TNF alpha and/or ETP was also studied by measuring the animal weight. Monotherapy with TNF alpha had no effect on tumor growth or proliferation. Treatment with ETP as a single agent, TNF alpha plus ETP applied concurrently and TNF alpha plus ETP two days later led to a slight inhibition of tumor growth and also to a slight decrease of the LI. In contrast to a monotherapy with TNF alpha, all therapeutic modalities containing ETP showed an increased toxic effect on the animals represented by a distinct weight loss. This suggests that the minute efficacy of the treatment observed could well be due solely to its toxicity. In contrast to two other studies, no additive or synergistic effect of the antineoplastic activity of TNF alpha and/or ETP was found. The intertumoral variation of human renal cell carcinomas could be one reason for the different results with this therapeutic regimen.

Answer 8:

Bibliographic Information

Effects of natural interferon alpha, natural tumor necrosis factor alpha and their combination on human mesothelioma xenografts in nude mice. Ohnuma T; Szrajer L; Holland J F; Kurimoto M; Minowada J Department of Neoplastic Diseases, Mount Sinai Medical Center, New York, NY 10029 Cancer immunology, immunotherapy : CII (1993), 36(1), 31-6. Journal code: 8605732. ISSN:0340-7004. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 8422665 AN 1993137249 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Effects of human natural interferon alpha (nIFN) alone, human natural tumor necrosis factor alpha (nTNF) alone and their combination (OH-1) were tested on three human mesothelioma lines implanted in nude mice. Tumors were transplanted subcutaneously by trocar on treatment day -12. nIFN was given intraperitoneally (i.p.) at a dose of 2 x 10(7) or 2 x 10(8) IU kg-1 day-1, 5 days a week for 3 weeks. nTNF was given i.p. at a dose of 2 x 10(7) or 2 x 10(8) U kg-1 day-1 in the same schedule as that of nIFN. Tumor diameters were serially measured and tumor volumes were calculated. Antitumor effects were assessed by two methods: comparison of final tumor volumes in treated and control groups (T/C), and changes in median average total tumor volume. The treatment produced no clinically discernible toxicities. nIFN had strong inhibitory activity against all three human mesothelioma lines. nTNF alone had modest activity only at the high dose used. The combination of the two produced activity essentially similar to that produced by nIFN alone. High-dose nIFN may have a role as an active agent in the treatment of patients with mesothelioma.

Answer 9:

Bibliographic Information

Differential antiproliferative activities of alpha- and gamma-interferon and tumor necrosis factor alone or in combinations against two prostate cancer xenografts transplanted in nude mice. van Moorselaar R J; van Stratum P; Borm G; Debruyne F M; Schalken J A Department of Urology, University Hospital Nijmegen, The Netherlands The Prostate (1991), 18(4), 331-44. Journal code: 8101368. ISSN:0270-4137. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 1905403 AN 1991279589 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

We have investigated the antiproliferative effects of recombinant human alpha- and gamma-Interferon (IFN) and recombinant human Tumor Necrosis Factor alpha (TNF) against the hormone-independently growing PC3 and DU145 prostatic tumor lines. Subcutaneous, peritumoral administration of the drugs was started 24 hours after subcutaneous implantation of 1-2 mm3 tumor pieces. IFN was given three times per week and TNF five times per week. IFN-alpha (dose-range 0.5-5 ng/gram bodyweight) had significant growth-inhibiting effects against the PC3 tumor, but showed no significant antitumor effects against the DU145 tumor. IFN-gamma monotherapy (dose-range 8-80 ng/gram bodyweight) was less effective than IFN-alpha. 500 ng/gram TNF produced growth inhibition of both tumors, whereas the lower dose (50 ng/g) was only effective against the PC3 tumor. IFN-alpha and -gamma combination treatment had significant antiproliferative effects against the PC3 tumor, but not against the DU145 tumor. Combinations of IFN-alpha and TNF were very effective against both xenografts; some combinations resulted in complete growth inhibition. IFN-gamma and TNF combinations also showed significant antitumor effects against both tumor lines. We therefore conclude that cytokine combination treatment may provide a new approach in the treatment of hormone-escaped prostatic tumors.

Answer 10:

Bibliographic Information

Antiproliferative and cytotoxic effects of single and combined treatment with tumor necrosis factor alpha and/or alpha interferon on a human renal cell carcinoma xenotransplanted into nu/nu mice: cell kinetic studies.
Baisch H; Otto U; Kloppel G Institute of Biophysics and Radiobiology, University of Hamburg, Federal Republic of Germany Cancer research (1990), 50(19), 6389-95. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 2400997 AN 1990381723 MEDLINE

Abstract

A human renal cell carcinoma serially transplanted into nude mice was treated with recombinant human tumor necrosis factor alpha (TNF-alpha), recombinant human alpha interferon (IFN-alpha), and a combination of both. All treatments resulted in a significantly reduced tumor growth. The greatest effect was obtained with the combination of TNF-alpha and IFN-alpha. This latter treatment completely eradicated tumors which were smaller than 50 mm3 at the beginning of treatment. Cell kinetic analysis using the bromodeoxyuridine technique and flow cytometry revealed a prolongation of the transition time through S-phase from 7.9 h in the case of control tumors to 10.5 h for tumors treated with IFN-alpha and TNF-alpha. Single treatment with either TNF-alpha or IFN-alpha had only minor effects. The bromodeoxyuridine labeling index was unaffected by IFN-alpha (16.6%; control, 15.2%) but was reduced to 12.1 and 11.7% when tumors were treated with TNF-alpha and IFN-alpha plus TNF-alpha, respectively. The calculated potential doubling times were 2.3 and 2.8 days, respectively, for tumors treated with TNF-alpha or IFN-alpha plus TNF-alpha. When treated with IFN-alpha, the potential doubling time (1.7 days) was similar to that of the control (1.6 days), indicating that the main effect of TNF-alpha was antiproliferative. Conversely, the calculated cell loss factors increased after IFN-alpha and combined treatment but not after TNF-alpha treatment. Combined treatment augmented cytotoxicity, but the cell kinetic characteristics of surviving cells remained similar to those of tumors treated with TNF-alpha alone. Histological analysis showed a distinctly reduced mitotic activity but no coagulative necroses after treatment with TNF-alpha. IFN-alpha and, in particular, IFN-alpha plus TNF-alpha induced cytoplasmic vacuolization, nuclear pyknosis, and cell death, which resulted in tumor regression.

These data suggest that, in this particular tumor model, TNF-alpha produces mainly antiproliferative effects, whereas IFN-alpha acts via cytotoxic mechanisms.